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综 述

MUCOSAL IMMUNE SYSTEM AND FERTILITY REGULATION IN MAMMAL AND HUMAN

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I. Introduction

Skin and mucosa are the first barriers or defense frontiers between internal and external milieu in mammals. Mucosa are the components of gastrointestinal, respiratory and genitourinary tracts. Mucosal associated lymphoid tissues (representing more than 70% of the total mammalian lymphoid elements are distributed in these tracts, and termed as mucosal immune system (Mestecky, 1987).

The mammalian gamete maturation and transport, binding and fusion between egg and sperm, transport of fertilized egg, embryo implantation and development are all conducted in the genital tracts. In the past decades, our knowledge on the relationship between mucosal (or local) immunity in genital tracts and infertility has been extensively increased (Jones, 1976; Schumacher, 1980; Alexander, 1988). The studies on this relationship are important not only in diagnosis and treatment of infertility and sexually transmissible diseases, but also in the development of contraceptive vaccine. The purpose of this paper is to introduce the recent progress in studies of mucosal immune system, immunological status of genital tracts in normal or infertile individuals and their potentials on fertility regulation.

I. Properties of Mucosal Immune System

The big differences between mucosal and nonmucosal (or systemic) immune systems exist in both humoral and cell-mediated immunities. High IgA levels are found in many external secretions including tears, saliva, colostrum, breast milk, and respiratory, gastrointestinal and genitourinary secretions. The daily production of IgA approximately 66 mg/kg/day for human exceeds the total amount of all other immunoglobulin classes. The majority of serum IgA in man is primarily produced in the bone marrow and does not enter external secretions in significant amounts, IgA in the secretions (secretory IgA, sIgA) is locally produced by plasma cells distributed in mucosal tissues. sIgA does not contribute significantly to the circulatory pool. The sIgA-producing system is also called common mucosal immune system or the secretory immune system that is relatively separated from systemic immune system.

To stimulate immune response in common mucosal immune system, foreign antigens penetrate through highly pinocytotic and phagocytotic membrane or microfold cells (M cell) covering gut-or bronchus associated lymphoreticular tissues (GALT or BALT), and interact with resident accessory and lymphoid cells. Besides the M cells, enterocytes also selectively present immunogenic molecules to T cell by the binding of the

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antigen with class Ⅰ MHC expressed on enterocytes, but non-immunogenic molecules (not binding to class Ⅰ) pass on to the lysosome compartment for terminal degration. On the other hand, enteroeytes absorb the peptide fragments digested by intraluminal protease through pinocytosis (Bland, 1988). The Peyer's patches located in small intestine are principal lymphoid tissue in the processes of immune response. IgA precursor B cells in GALT or BALT enter the recirculating lymphocyte pool and regional lymph nodes through the thoracic duct and bloodstream, and then home to the lamina propia of intestinal, respiratory and genitourinary tracts, and salivary, lachrymal and mammary glands, where they differentiate into IgA producing plasma cells. The epithelial cells lining the tract lumen and gland ducts produce a glycoprotein, IgA Fc receptor, also called secretory component which binds to IgA dimer and forms sIgA. The sIgA is internalized by the epithelial cells, and then is exocytosed into the secretions. The sIgA in the secretions can inhibit antigen attachment to the mucosa, combines with and neutralizes antigens or pathogens (Mestecky, 1987, Hogg, 1988). This concept of a common mucosa immune system is supported not only by extensive animal studies (Mestecky, 1987), but also by the recent studies on humans (Czerkinsky *et al.*, 1987).

The cells involved in the regulation of these processes include suppressor T cell (Tc/s), helper T cell (Th), contrasuppressor cell (Tcs) and anti-suppressor cell. Tcs may non-specifically block the inhibition of Th by Tc/s, can bind with a *Vicia villosa* lectin, and express CD3, CD8 and class Ⅰ MHC on the cell surface; thus Tcs is also called $CD8^+$, VV^+ cells (Mestecky, 1987; Lehner, 1986). The function of anti-suppression inducer T cells is similar to Tcs, but the regulatory factor secreted by these cells occurs within 6 hours or less of a primary immunization rather than after repeated antigenic stimulations. A complex of immunoglobulin and antigen forms in presence of the factor. This complex binds to and activates the anti-suppressor effector T cells, which eventually leads to the inhibition of suppressor cell function. These cells from Peyer's patches can selectively promote IgA synthesis (Ernst *et al.*, 1988). In addition, IL-5 produced by Th_2 cells may enhance the IgA synthesis in B cells, but not stimulate the proliferation of B cells. IL-4 synergically enhances the effect of IL-5 on the production of IgA (Beagley *et al.*, 1988).

As for another arm of immune system, cell-mediated immunity, the great progress in the studies on T cell antigen receptors (TCR) has been achieved. A particularly intriguing hypothesis concerning the differential anatomic distribution of receptor TCR1 (γ,δ) and TCR2 (α, β) bearing T lymphocytes has beeen presented by Janeway and associates (Janeway *et al.*, 1988). TCR1 may arise first in phylogeny as well as in ontogeny. TCR1-bearing T cells are largely distributed in thymus epidermis, intestinal epithelia and other mucosal tissues, and mediate immunological surveillance of epithelia and other mucosal tissues, monitoring the integrity of the cell layers that separate the internal from the external milieu; TCR2-bearing cells are responsible for surveillance of the internal milieu by circulation through lymphoid organs. Cells bearing TCR1 may recognize a novel class Ⅰ MHC expressed on infected and transformed epithelia but not on normal one. Much evidence on distribution, migration and function of TCR1-bearing lymphocytes is needed to prove this hypothesis (Carter *et al.*, 1988; Meuer, 1989).

These phenomena described above raises a question of how the particular lymphocytes home to specific sites. Recent studies have yielded substantial information on the regulation and specificities of lympocyte-endothelial adhesion mechanisms that direct lymphocyte migration into particular tissues. To enter the various lymphoid tissues (except spleen) involved in recirculation, lymphocytes have to cross the endothelial vascular lining. The lymphocyte extravasation occurs at specialized post capillary vascular sites called high-endothelial venules (HEVs). The lymphocyte-HEV recognition and adhesion are mainly carried out by the homing receptors on different lymphocytes, tissue-specific vascular addressins on HEV and accessory adhesion molecules (LFA-1, ICAM-1, endothelial-leukocyte adhesion molecule etc.). The regulation of the adhesiveness between the lymphocytes and HEV is controlled by cytokines (IL-1, TNF, IFN-γ and others) (Duijvestijn, 1989).

Ⅱ. Characteristics of Mucosal Immune System in Female Genital Tracts

In woman genital tract, the immunoglobulin levels vary with the menstrual cycle, and the secretion of immunoglobulins is modulated by reproductive hormone. The ratio of IgA to IgG is higher than that found in serum (Schumacher, 1980). Using the radial diffusion method, Tauber *et al.* quantitatively measured the humoral components that were released by isolated mucosa areas. The mucosa were collected from 36 women with regular menstrual cycles at different phases. The high concentration of immunoglobulins in the mucosa of the cervix and uterus during the periovulatory phase were found (Table 1). Both ends of the genital

Tab. 1. Cyclic variation of IgG and IgA from genital tract mucosa

Ig	Cervix			Uterus			Fallopian tube		
	F	P	L	F	P	L	F	P	L
IgG	3.88±0.25	4.92±0.32	2.41±0.23	2.41±0.18	4.66±0.43	3.24±0.22	3.78±0.21	1.66±0.21	2.70±0.16
IgA	0.33±0.05	0.63±0.06	0.39±0.06	0.25±0.03	0.49±0.05	0.33±0.01	0.37±0.069	0.12±0.015	0.17±0.015

The values are expressed as μg/mg (mean±SEM) of tissues isolated during follicular (F), periovalatory (P) and luteal (L) phases. The data are from Tauber *et al.*, 1985.

tract (the cervix and the fimbriated ends of the tubes) were high in level of immunoglobulins throughout the cycle, there by the chance for infectious agents to enter or exit the tract decreased. The secretory component was detectable in cervix, uterus and fallopian tubes (Tauber *et al.*, 1985; Krajci *et al.*, 1989). The total complement activity was higher in the internal and than in other part of the tract. The C3 component was higbest in the cervical canal, internal os and first part of the uterine cavity (Tauber *et al.*, 1985). The levels of sIgA and lactoferrin were higher in cervical mucus at the first trimester of gestation in women with normal pregnancy as compared with infertile and healthy women (Chernisnov *et al.*, 1989). The counts of B cells bearing different surface immunoglobulins on cryostat sections were quantitatively evaluated by Rebello *et al.* (Schumber, 1980). A predominance of IgA producing cells appears in the cervix. Mestecky *et al.* (1989) found that the distribution of IgA1 and IgA2 cells in uterine cervical glands resembled that of the intestine(approximately equal numbers of IgA1 and IgA2 cells), but significantly differed from that of other mucosal sites where IgA1-producing cells predominate (Mestecky *et al.*, 1989).

Recently, Wira and associates investigated the regulatory mechanisms of specific IgA and IgG antibodies in the secretions of female reproductive tract of rats. Peyer's patch and intraperitoneal immunization and boost with sheep red blood cells (SRBC) stimulated the appearance of specific IgA antibodies in uterine and vaginal secretions of uterine-ligated animals. IgG antibodies were also induced in uterine but not in vaginal secretions, subcutaneous immunization and boost only elicited a weak IgA uterine and IgG vaginal response. When ovariectomized rats received primary and/or secondary Peyer's patch immunizations with administration of estradiol (1μg/day/rat) daily for 3 days, uterine IgA and IgG antibodies to SRBC and secretory component increased, but the levels of vaginal IgA and IgG antibodies as well as secretory component level decreased. The action of estradiol on vaginal components appears to be different from uterine influence. The reason of these differences is not clear (Wira, 1985; Wira, 1987). Several studies have shown that IgA lymphoblasts can migrate into the rat genital tract during the estrous cycle and response to hormone treatment (McDermott *et al.*, 1980).

The distribution of leukocytes and lymphocyte subpopulations in endometrium has been investigated by

several groups. Immunohistochemical studies of the endometrium from 150 fertile women has shown that not only T and B cells, but also macrophages, granulocytes, NK cells, IL-2 receptor positive cells are located in. Most lymphocytes are distributed between the epithelial cells, as aggregates around the glands, and diffuse in the stroma. The typical variations of the number of lymphocytes occur during the menstrual cycle. The amount of pan-T and T suppressor cells increase during the ovulation phase, decrease afterwards, and rise once again during the late luteal phase. The number of T helper cells is low and their changes during the cycle are insignificant (Donat, 1989). Another group has shown that the Th, Ts ratio is significantly elevated during the periovulatory phase attributable to a decreased density of Tc/s in the human endometrium (Hill, unpublished data). The endometrial granulated lymphocytes (eGL) ($CD2^{+/-}$, $NKH1^{+}$, $CD7^{+/-}$, $CD38^{+}$, $CD16^{-}$, $Leu7^{-}$, $CD3^{-}$) can be detected in first trimester human decidua and in late secretory phase of endometrium. eGL purified from first trimester human decidua exhibits cytotoxicity activity in a K562 chromium release assey. The CD3 positive T cells are a relatively minor proportion of endometrial lymphocytes. The majority of T cells are CD8-positive and TCR2-bearing cells, and less than 10% of T cells are TCR1-bearing cells (Bulmer, 1989).

At fetal-maternal interface, the placental macrophages and lymphoid cells produce various interleukins (IL-1, IL-3) which contribute to the specialization of the maternal immune response to develop allogeneic embryo. Placenta cells proliferate more extensively in the presence of IL-1 and IL-3, in contrast, interferon (IFN, 1,500—150,000 units/ml) and tumor necrosis factor (TNF, 100—10,000 units/ml) significantly inhibit trophoblast proliferation. B cell growth factor (IL-5) produced by T cells stimulate proliferation at low concentration (13—130 units/ml), but inhibit trophoblast proliferation at the high concentration (650 units/ml) (Toder, 1988; Toder et al., 1989; Hill, 1988). Furthermore, local immunosuppressive factors (trophoblast, decidual cells, placenta hormones, progesterone etc.) can inhibit IL-2 production and impair IL-2 functioning.

Two types of non-Tc/s lymphocytes have been discovered in human and murine pregnancy uteri. One of them is the large progesterone-dependent suppression cells located in endometrium. Its activity becomes apparent after ovulation. The large suppressor cells and their products (at molecular weight of 100—300 kda) may block maternal sensitization to sperm and embryo antigens. The second type of suppression cell, a small cell, exists in decidua of pregnancy uterus. Its products at molecular weight of 43 and 21 kda inhibit the action of IL-2 by preventing IL-2 from binding with IL-2 receptor. The decidual suppressor cell activity declines apparently as term approaches. The large and small suppression cells and their products may block maternal rejection to fetal allograft, and maintain the survival of human fetal (Daya, 1988).

Ⅳ. Local Autoimmunity in Endometriosis and Recurrent Spontaneous Abortion

About 40%—70% of women with endometriosis are infertile, and 1%—7% of women during their reproductive lives may suffer from the endometriosis. The endometriosis is also often found in nonhuman primates (Ben, 1978). Since the increased incidence of autoantibodies IgG and IgA to ovarian and endometrial tissues in patients with endometriosis has been reported by Mathur and the others, the concept of autoimmunity in endometriosis is gradually accepted (El-Roeiy, 1988). Autoantibodies to endometrial antigens are observed in the serum, peritoneal fluid and endometrial implants of patients with endometriosis. A recent study has shown that the humoral and local endometrial antibodies detected in patients with endometriosis is directed against endometrial antigens with molecular weight of 26 and 34 kda (Mathur *et al.*, 1988). A new simple method in detection of specific antibodies to endometrial tissue has been developed by several groups (Starkey *et al.*, 1989).

Recurrent spontaneous abortion (RSA) is a common and important clinical problem. Approximately 70%

—80% of human pregnancies do not reach fetal viability. About 50%—60% are lost prior to the first missed menses, and about 20% of all conceptions end in clinically recognizable spontaneous abortion (Edmonds *et al.*, 1982). Immunological factors may play very important roles in some unexplained RSA. For instance, HLA sharing, cellular and humoral immunities to embryo, sperm or trophoblast antigens have been shown to be involved in RSA by in vivo or in vitro human and animal studies (Hill, 1988).

V. Local Immune Response To Sperm

Immunoglobulins of IgG and IgA are often detectable in human seminal plasma. These antibodies may be produced locally by plasma cells residing in male tracts or transuded through prostate or other accessory glands. The complement C3 and C4 are rarely found in seminal plasma of normal fertile men. Immunosuppressive effects of semen have been extensively studied by many investigators. The reported effects include: (1) inhibition of T and B lymphocytes to proliferate in response to mitogen. (2) impairment of phagocytic function of macrophages and polymorphonuclear leukocytes. (3) impairment of the ability of NK cells and cytotoxic T cells to destroy tumor and virally infected target cells. (4) anti-complement effects could serve to protect spermatozoa from antibody-mediated lysis. Naturally, immunosuppressive factors from male reproductive tract protect the sperm from the attack of female or male immune response. On the other hand, individuals lacking such factors and their spouse could have the problem of immunologic infertility. The sexually transmissible diseases (STD) (gonorrhea, syphilis, chlamidia, AIDS and hepatitis B) are probably promoted by these immunosuppressive factors. They may also facilitate the growth of the very common malignancy (prostatic cancer in man and cervical cancer in women) (Alexander, 1987).

Numerous viable lymphocytes and monocytes are present in normal human semen. After vasectomy, their numbers are significantly reduced, therefore, these cells appear to originate from efferent ducts and/or epididymis. The role of macrophages in semen may be removal of immotile sperm from the insemination site. Much higher numbers of granulocytes, monocytes and lymphocyte subsets were found in the semen from infertile group (Wolf, 1988; Alexander, 1987).

Clinical and experimental investigations have shown that local immunity to sperm in genital tracts may play very important roles in infertility and subfertility. The reduced ability of sperm from infertile men to penetrate cervical mucus was caused by locally produced IgA (Jager *et al.*, 1980). Witkin *et al.* (1982) reported a case of a subfertile man who had IgA antibodies to spermatozoa in his seminal and prostatic fluids. The antisperm antibody classes in serum, peritoneal fluid (PF), uterotubal lavage (UL) and vaginal fluid(VF)from 10 women with positive serum antibodies to sperm were compared by indirect immunobead test. The positive rate of IgA in PF (2/6) was similar to that in serum (3/10), whereas those in UL (6/7) and VF (5/5) were much higher than in serum and PF (Bronson, 1988). The antisperm antibodies of IgA class in human cervical mucus were observed in 12.7% of 102 patients by immunobead test (IBT). A strong correlation between the IgA-IBT and the presence of complement-dependent sperm immobilization in serum has been found (Clarke *et al.*, 1984). A further study showed that 7 (8.9%) of 78 infertile women were positive for IgG and/or IgA classes in bromelin-treated cervical mucus; and none (0/35) were found positive for IgM, 57% of the positive samples contained both IgG and IgA classes, the rest samples contained IgA alone (Clarke, 1984). In a large group of infertile women, 28% were antisperm antibody positive in their cervical mucus, but no one positive in the serum. These data suggest that local immune response to sperm in women often play an important role in woman infertility.

The local production within the genital tract of men was also suggested by the following studies. Immunoglobulins were detected on the sperm surfaces in 13% of 1825 semen specimens from infertile couples. Both serum and semen specimens were studied in 846 men; 20% of them were found to have sperm reactive antibodies in their blood without any detected antibodies on spermatozoa, and 15% of men were found to

have autoantibodies on the sperm surface, but none were detected in serum (Bronson, 1988). Antisperm IgA and IgG isotypes in semen or on sperm surface were detected in roughly equal frequency (Clarke *et al.*, 1985). The antisperm antibody classes in seminal plasma from the vas-occluded and spontaneously infertile men with positive serum antisperm antibodies, and from spouses of recurrent abortion patients were detected in our laboratory with enzyme linked immunosorbent assay (ELISA). The percentages of the patients with IgA, IgG and IgM are 69.1, 54.4 and 52.9, respectively (Chen *et al.*, 1990). These results indicate that the need to study the semen directly rather than rely solely on serologic test for the diagnosis of immunological male infertility. For the individual with immunological infertility, it is difficult to know the precise source for the production of antisperm antibodies in semen. The possible sources include epididymis, seminal vesicle and prostate or transudates through these compartments from blood.

It is difficult to collect and purify antisperm IgA from human or animal secretions to confirm the effect of IgA alone on sperm function, therefore, the production of monoclonal IgAs to sperm and study of their effects on sperm function and fertilization are needed and will be helpful for the design of delivery system of contraceptive vaccines.

Ⅵ. Can One Control Mucosal Immune System to Regulate Fertility

As described above, mammalian mucosal immune system and its targets in genital tracts interact each other to maintain the successful reproduction in normal status. The fertility may fail when the interaction is in out of order. The immunological infertility caused by antisperm antibodies can be treated with corticosteroids (Alexander *et al.*, 1983) or in vitro fertilization (Cohen *et al.*, 1985). Unfortunately, no treatmnt is a satisfied approach to solve the problem up to now.

On the other hand, the rationale of immunological infertily in human and animals can be useful in the development of birth control vaccine. As I mentioned, the mucosal immune responses to the targets in genital tracts play an important role in infertility. Many investigations have shown that local stimulation with antigens is much more effective than systemic immunization to induce mucosal immune responses. Furthermore, from the view of practial application, oral immunization is the simplest route of administration, and is the most acceptable particularly in developing countries, because oral immunization does not require well-trained health personnel to inject the vaccine, and large number of peoples can be vacrinated simultaneously.

Oral immunization in human and animals can induce the production of sIgA and IgG antibodies in lachrymal, parotid, salivary and mammary glands (Mestecky, 1987). Since 1960's, over 16 live or inactivated viral vaccines for animal diseases and 3 vaccines for human diseases have become availble (Table 2) (Ogra *et al.*, 1988).

Tab.2. Available viral vaccines which can be administrated via the mucosal route

Human	Polio	Non-human	Infectious bronchiolitis
	Rubella		Fowl pox
	Adenovirus		Infectious laryngotracheitis
	Rotavirus*		Encephalomyelitis
	Influenza*		Marek's disease
	Measles*		Rotavirus
			Duck hepatitis
			Rabies

* Candidate vaccines
From Ogra *et al.*, 1988.

Several antigen delivery systems effective for induction of mucosal immune respone have been approached in animal models. Genetically engineered bacteria, avirulent *Salmonella typhimurium*, can be transformed with a plasmid carrying the cloned S fimbriae genes of a uropathogenic *Escherichia coli* (Schmidt *et al.*, 1989) or with a plasmid expressing *Streptococcus mutans* colonization protein antigens (Curtiss *et al.*, 1988). Oral immunization in rats or mice with live engineered bacteria are often effective in stimulating secretory immune response against both *S. typhimurium* and the products of foreign recombinant genes from *E. coli* or *S. mutans*. The gene of influenza nucleoprotein was also harbored in *S. tyhimurium*. The generation of anti-viral immunity in serum has been induced in mice by oral administration of live recombinant bacteria (Tile *et al.*, 1989). Another sophisticated approach involves coating of antigens in gelatin capsules with substances that are soluble only at the alkaline pH of the small intestine. This method has been successfully used in human oral immunization with bacteria or virusses (Mesteckcy, 1987). The third approach is to incorporate antigens into liposomes. The oral immunization of liposome-coated ovalbumin. *E. coli* wall extract, proteins and carbohydrate derived from *S. mutans* have been employed in animal models (Clarke *et al.*, 1989). Other orally administered adjuvants, such as muramyl dipeptide (MDP) cholera toxin B subunit and others have been also used for enhancing mucosal immune responses.

Using sheep red blood cells in rat model system, Wira and associates found that gastrointestinal and uterine immunization can stimulate the production of specific antibodies IgA and IgG as well as SC in female genital tract (Wira *et al.*, 1989; Wira, 1986).

Since Curtis and Ryan(1982) reported that gastrointestinal immunization of CD-1 mice with murine sperm was successful in reducing fertility (Curtis, 1982), controversial results have been obtained by different groups. NZBW female rats were intragastrically immunized with homologous epididymal sperm, the short to long term infertility was induced, and the infertility was associated with an early rise of genital secretory IgA antisperm antibody (Allardyce, 1984).Parr and Parr immunized outbred female mice of ICR strain with washed murine sperm. In the groups of intragastric, intraduodenal, intravaginal. intrapeyer's patch or combined routes, there is no detectable IgG or IgA in plasma, vaginal washings and on uterine and oviduct sperm, there were no significant differences in the numbers of pups between experimental and control groups (Parr, 1986). The disparate results may be caused by the different mouse strains used for their studies.

Tab.3. The specific efficiency (SE) of antisperm IgA and IgG-positive hybridomas (numbers of positive hybridomas/numbers in 10^8 of spleen or Peyer's patch cells used for fusion)

	IP	IPP	IL		IL+O	IPP+O	O
	Spl	Spl	Spl	PP	Spl	Spl	Spl
IgA	2.25	48.95	31.28	159.40	21.5	13	4.5
IgG	53.96	47.38	127.41	113.29	109.5	16	3.5

The mice were intraperitoneally (IP), or intrapeyer's patche (IPP), or intralumen of small intestine (IL) and/or intragastrically (O) immunized. The hybridomas were obtained with fusion of SP2 and lymphocytes from spleen (Spl) or Peyer's patches (PP).

Recent studies in our laboratory have demonstrated that the high level of anti-human sperm IgA were detected in serum from the mice immunized through lumen of small intestine plus intragastric tube or Peyer's patches plus intragastric tube with washed human sperm. The highest density of the cells producing anti-human sperm antibody IgA was found in murine Peyer's patches by the immunization of intralumen of small

intestine or intrapeyer s patch (Ma *et al.*, 1989) (Table 3). Similar results was also seen in the immunization of mice with murine sperm specific antigen LDH-C4 (Feng *et al.*, 1989).

In summary, as the delivery system of a vaccine, oral immunization with live genetically engineered bacteria is the most attractive method not only in the prevention of STD, but also in the developmemt of birth control vaccine. The oral contraceptive vaccine for sperm antigens is particularly preferred.

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哺乳类动物和人的粘膜免疫系统与生育力调节

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中 文 摘 要

皮肤和粘膜是哺乳类动物和人体的内外环境之间的第一道屏障或第一道防线。粘膜是消化道，呼吸道和泌尿生殖道的重要组成部份。在粘膜系统大约集中了70%的淋巴组织。哺乳类动物的配子成熟，运输，精卵子的结合和融合，受精卵的运输，胚泡着床等等，都是在生殖道内进行的。因此，研究生殖道的粘膜免疫系统在不育的诊断和治疗，性传染疾病的控制，避孕疫苗的研究等方面，都有很重要的意义。

粘膜免疫系统有几个显著的特点：首先，在抗体成份方面，以 IgA 为主，IgA 的分泌量约占全身各种抗体成份的60%以上。为了刺激粘膜的体液免疫反应，局部免疫的效果最佳。参与粘膜免疫调节的细胞有T辅助细胞，T杀伤和抑制细胞，反抑制细胞，抗抑制细胞。其次在细胞免疫方面，粘膜系统有许多TCR1 T细胞，它们在粘膜免疫方面可能具有重要的功能。粘膜系统的免疫细胞的特有分布是通过细胞表面的许多受体和配体的相互作用来实现的。雌性生殖道的粘膜免疫系统的反应常与激素水平有关，如雌二醇的升高常伴随 IgA的升高，孕酮的存在常有抑制 IgA 产生的作用。此外，在妊娠子宫内发现有许多特殊的抑制细胞和其他许多抑制因子。

在某些不孕患者的精浆内可测定到抗精子的IgA 和IgG。精浆内存在许多免疫细胞抑制因子和许多免疫细胞。不育患者的免疫细胞的数量增高。雌性生殖道内 IgA 型抗精子抗体的存在与不育的关系十分密切。以单克隆 IgA 研究抗精子局部免疫的作用是很重要的课题。通过控制粘膜免疫系统来调节生育力。应用免疫抑制药物可以治疗某些免疫性不育。

对于免疫避孕来说，口服避孕疫苗的研制不仅是必要的，也是可能的。动物实验表明，口服疫苗可以刺激局部IgA 和 IgG 的产生。基因工程细菌也许是最简便有效的抗精子避孕疫苗的载体。其它一些口服疫苗的投药系统也正在研制之中。口服疫苗同时也是某些性传播疾病（如艾滋病，乙肝等）的重要预防手段。

关键词：粘膜免疫系统，生育力调节，哺乳动物，人类